

benefit of United States Patent Application Serial No. 60/094,425, filed July 28, 1998, the entire contents of each of which is incorporated herein by reference.

Please delete the paragraph beginning at page 1, line 12, and insert the following:

A primary strategy for rotavirus vaccine development has been based on a "Jennerian" approach, which takes advantage of the antigenic relatedness of human and animal rotaviruses and the diminished virulence of animal rotavirus strains in humans. Kapikian *et al.*, in *Vaccines 88*, Chanock *et al.*, eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pp. 151-159 (1988). Several candidate live oral rotavirus vaccines have been developed using this approach, where an antigenically-related live virus derived from a nonhuman host is used as a vaccine for immunization against its human virus counterpart. Examples of animal rotaviruses that have been used to vaccinate humans include bovine rotavirus strain NCDV (RIT4237, Vesikari *et al.*, Lancet, 2:807-811 (1983)), bovine rotavirus strain WC3 (Clark *et al.*, Am. J. Dis. Child., 140:350-356 (1986)) and rhesus monkey rotavirus (RRV) strain MMU 18006 (U.S. Patent 4,571,385, Kapikian *et al.*, *Vaccines85*, eds., Lerner *et al.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pp. 357-367 (1985)).

Please delete the paragraph beginning at page 3, line 17 and insert the following:

The general experience with monovalent and quadrivalent human x rhesus rotavirus reassortant vaccines has been that a transient low-level febrile episode occurs in about one-third of young infants 3 to 4 days after vaccination. Bernstein *et al.*, JAMA 273:1191-1196 (1995); Flores *et al.*, Lancet 336:330-334 (1995); Perez-Schael *et al.*, J. Clin. Microbiol. 28:553-558 (1990); Flores *et al.*, J. Clin. Microbiol. 31:2439-2445 (1990); Halsey *et al.*, J. Infect Dis. 158:1261-1267 (1988); Taniguichi *et al.*, J. Clin. Microbiol. 29:483-487 (1991); Simasathien *et al.*, Pediatr. Infect. Dis. J. 13:590-596 (1994); Madore *et al.*, J. Infect. Dis. 166:235-243 (1992); and Joensuu *et al.*, Lancet 350:1205-1209 (1997).

Please delete the paragraph beginning at page 3, line 25, and insert the following:

Results of studies in humans with bovine rotavirus strains NCDV and WC3 (VP7 serotype 6) indicate that these particular bovine rotavirus strains do not appear to cause fever or other reactions. It should be noted that serotype 6 VP7 is not known to be present on human rotaviruses that are important in human rotavirus disease. Also, a bovine rotavirus was not found to be as immunogenic as the rhesus rotavirus when administered to humans. The bovine rotavirus strain NCDV (RIT4237 vaccine) has been evaluated in more than five efficacy trials in infants and young children. In these trials, the bovine RIT4237 vaccine was administered at a dose range of $10^{7.8}$ to $10^{8.3}$ tissue culture infectious doses₅₀ (TCID₅₀), with the usual dosage exceeding $10^{8.0}$ TCID₅₀. Also, in a dose-response study, Vesikari *et al.*, Ped. Infect. Dis., 4:622-625 (1985)) observed that 15% (2/13) of four- to six- month old infants developed a homotypic antibody response when the vaccine was administered at a dose of $10^{6.3}$ TCID₅₀; 71% (10/14) when administered at a dose of $10^{7.2}$ TCID₅₀, and 100% when administered at a dose of $10^{8.3}$ TCID₅₀. Thus, the dose for this bovine rotavirus strain that produced an optimal immunogenicity was determined to be in the range of $10^{8.0}$ TCID₅₀.

At page 13, please delete the paragraph beginning at line 15, and insert the following:

Human x bovine reassortant rotavirus strains representing VP7 serotypes 1, 2, 3 and 4 were derived from the bovine UK Compton (UK) strain and from human rotavirus strains D (VP7 serotype 1, ATCC VR-970), DS-1 (VP7 serotype 2; Wyatt *et al.*, Perspect. Virol. 10:121-145 (1978)) and P (VP7 serotype 3; Wyatt *et al.*, Science 207:189-171 (1980)), and ST3 (VP7 serotype 4; Banatvala *et al.*, J. Am. Vet. Med. Assoc. 173:527-530 (1978)). Human rotavirus strains D, DS-1, and P were recovered from stools of children hospitalized with diarrhea; Strains D and DS-1 were propagated and passaged in gnotobiotic calves (Wyatt *et al.*, 1978, supra; and Midthun *et al.*, 1985, J. Virol. 53:949-954) and later grown only in tissue culture, while strain P was grown only